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Fibrin glue for pilonidal sinus disease (Review)

Lund J, Tou S, Doleman B, Williams JP

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[Intervention Review]

Fibrin glue for pilonidal sinus disease

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ABSTRACT

Background

Pilonidal sinus disease is a common condition that mainly affects young adults. This condition can cause significant pain and impairment of normal activities. No consensus currently exists on the optimum treatment for pilonidal sinus and current therapies have various advantages and disadvantages. Fibrin glue has emerged as a potential treatment as both monotherapy and an adjunct to surgery.

Objectives

To assess the effects of fibrin glue alone or in combination with surgery compared with surgery alone in the treatment of pilonidal sinus disease.

Search methods

In December 2016 we searched: the Cochrane Wounds Specialised Register; CENTRAL; MEDLINE; Embase and CINAHL Plus. We also searched clinical trials registries and conference proceedings for ongoing and unpublished studies and scanned reference lists to identify additional studies. There were no restrictions with respect to language, date of publication or study setting.

Selection criteria

We included randomised controlled trials (RCTs) only. We included studies involving participants of all ages and studies conducted in any setting. We considered studies involving people with both new and recurrent pilonidal sinus. We included studies which evaluated fibrin glue monotherapy or as an adjunct to surgery.

Data collection and analysis

Two study authors independently extracted data and assessed risk of bias. We used standard methods expected by Cochrane.

Main results

We included four RCTs with 253 participants, all were at risk of bias. One unpublished study evaluated fibrin glue monotherapy compared with Bascom's procedure, two studies evaluated fibrin glue as an adjunct to Limberg flap and one study evaluated fibrin glue as an adjunct to Karydakis flap.

For fibrin glue monotherapy compared with Bascom's procedure, there were no data available for the primary outcomes of time to healing and adverse events. There was low-quality evidence of less pain on day one after the procedure with fibrin glue monotherapy compared with Bascom's procedure (mean difference (MD) -2.50, 95% confidence interval (CI) -4.03 to -0.97) (evidence downgraded twice for risk of performance and detection bias). Fibrin glue may reduce the time taken to return to normal activities compared with Bascom's procedure

(mean time 42 days with surgery and 7 days with glue, MD -34.80 days, 95% CI -66.82 days to -2.78 days) (very low-quality evidence, downgraded as above and for imprecision).

Fibrin glue as an adjunct to the Limberg flap may reduce the healing time from 22 to 8 days compared with the Limberg flap alone (MD -13.95 days, 95% CI -16.76 days to -11.14 days) (very low-quality evidence, downgraded twice for risk of selection, performance and detection bias and imprecision). It is uncertain whether use of fibrin glue affects the incidence of postoperative seroma (an adverse event) (risk ratio (RR) 0.27, 95% CI 0.05 to 1.61; very low-quality evidence, downgraded twice for risk of selection, performance and detection bias and imprecision). There was low-quality evidence that fibrin glue, as an adjunct to Limberg flap, may reduce postoperative pain (median 2 versus 4; P < 0.001) and time to return to normal activities (median 8 days versus 17 days; P < 0.001). The addition of fibrin glue to the Limberg flap may reduce the length of hospital stay (MD -1.69 days, 95% CI -2.08 days to -1.29 days) (very low-quality evidence, downgraded twice for risk of selection, performance and detection bias and for unexplained heterogeneity).

A single RCT evaluating fibrin glue as an adjunct to the Karydakis flap did not report data for the primary outcome of time to healing. It is uncertain whether fibrin glue with the Karydakis flap affects the incidence of postoperative seroma (adverse event) (RR 3.00, 95% CI 0.67 to 13.46) (very low-quality evidence, downgraded twice for risk of selection, performance and detection bias and for imprecision). Fibrin glue as an adjunct to Karydakis flap may reduce length of stay but this is highly uncertain (mean 2 days versus 3.7 days; P < 0.001, low-quality evidence downgraded twice for risk of selection, performance and detection bias).

Authors' conclusions

Current evidence is uncertain regarding any benefits associated with fibrin glue either as monotherapy or as an adjunct to surgery for people with pilonidal sinus disease. We identified only four RCTs and each was small and at risk of bias resulting in very low-quality evidence for the primary outcomes of time to healing and adverse events. Future studies should enrol many more participants, ensure adequate randomisation and blinding, whilst measuring clinically relevant outcomes.

PLAIN LANGUAGE SUMMARY

Fibrin glue for pilonidal sinus disease

Review question

We reviewed the evidence regarding the effectiveness of fibrin glue, used on its own or with surgery, in the treatment of pilonidal sinus disease.

Background

Pilonidal sinus disease is a common condition mainly affecting young adults. The condition develops following an infection in the groove between the buttocks. The infection can cause fluid collections or a sinus (a channel under the skin) to form. Young men are more likely to be affected, and other risk factors include obesity, poor hygiene and prolonged sitting. Extensive body hair is also a factor as ingrowing hair follicles are thought to make the condition worse. The condition causes pain and often requires time off work. This affects patients' quality of life and may cause loss of earnings.

Pilonidal sinus disease is normally treated with a small operation. Fibrin glue, a naturally-occurring glue-like gel, can also be used as an alternative to, or in addition to surgery. We looked for evidence as to whether fibrin glue can speed up the healing time for this type of wound. We also wanted to find out if the treatment affected other outcomes such as pain, infection and return of the pilonidal sinus following the procedure, and whether it had any side effects (fluid collections or allergic reactions).

Study characteristics

In December 2016 we searched for randomised controlled trials involving participants of any age or sex, whose pilonidal sinus had been treated with fibrin glue, either on its own or with surgery. We found four studies that included 253 participants, the majority of whom were male. Fibrin glue on its own was compared with surgery in one study. In three studies fibrin glue was applied during surgery and compared with surgery on its own. There were problems with the design and conduct of all four studies which mean that their results are very uncertain.

Key results

It is not known whether fibrin glue on its own affects time to healing and adverse events compared with a type of surgery (Bascom's procedure). Fibrin glue may result in less pain on the first day after the procedure compared with Bascom's procedure.

When fibrin glue is used alongside a type of surgery called the Limberg flap it may reduce the healing time by approximately 14 days compared with the surgery on its own, however this finding is highly uncertain as the evidence is very low-quality. It is uncertain whether using the fibrin glue alongside the Limberg flap affects the incidence of a complication called seroma (a collection of fluid) but it may reduce postoperative pain (this evidence is low-quality and therefore quite uncertain) and may reduce time to return to normal activities (low-quality evidence) and length of hospital stay (this was very low-quality evidence and therefore very uncertain).

One study evaluated the effect of adding fibrin glue to a type of surgery called the Karydakis flap. It is not clear from this study whether using the glue affects time to healing or the incidence of seroma. Using the fibrin glue with the Karydakis flap may reduce length of hospital stay compared with surgery alone but again this is low-quality evidence.

Quality of the evidence

The quality of evidence for all outcomes was low or very low, mainly due to problems with the ways the studies were conducted and also the uncertainty in the results because of the small numbers of participants in the studies. This means we cannot be confident of the effects of fibrin glue on any of these outcomes and more, better quality and larger studies are required.

This plain language summary is up to date as of December 2016.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Fibrin glue compared with Bascom's procedure for pilonidal sinus

Fibrin glue compared with Bascom's procedure for pilonidal sinus

Patient or population: adults with pilonidal sinus

Settings: secondary care

Intervention: fibrin glue

Comparison: Bascom's procedure

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Bascom's procedure	Fibrin glue				
Time to healing (days)	Not reported					
Adverse events (seroma or allergic reaction)	Not reported					

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 2. Limberg flap plus fibrin glue compared with Limberg flap for pilonidal sinus

Limberg flap plus fibrin glue compared with Limberg flap for pilonidal sinus

Patient or population: Men with pilonidal sinus

Settings: secondary care

Intervention: Limberg flap plus fibrin glue

Comparison: Limberg flap

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Limberg flap	Limberg flap plus fibrin glue				
Time to healing (days)	The time to healing with Limberg flap plus fibrin glue was on average, 13.95 days quicker (16.76 days to 11.14 days quicker)		-	132 (1 study)	⊕⊝⊝⊝ **very low[1]**	The mean time to healing with Limberg flap alone was 22.08 days
Adverse event (seroma)	61 per 1000	17 per 1000 (3 to 99)	RR 0.27 (0.05 to 1.63)	164 (2 studies)	⊕⊝⊝⊝ **very low[2]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** mean difference; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels for risk of bias (randomisation, blinding and other bias, double downgrade) and imprecision.
[2]Downgraded three levels for risk of bias (randomisation, allocation concealment, blinding and other bias, double downgrade) and imprecision.

Summary of findings 3. Karydakis flap plus fibrin glue compared with Karydakis flap and drain for pilonidal sinus

Karydakis flap plus fibrin glue compared with Karydakis flap and drain for pilonidal sinus

Patient or population: Men with pilonidal sinus

Settings: Secondary care

Intervention: Karydakis flap plus fibrin glue

Comparison: Karydakis flap and drain

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Karydakis flap and drain	Karydakis flap plus fibrin glue			
Time to healing (days)	Not reported				
Adverse event (seroma)	80 per 1000	240 per 1000 (54 to 1000)	RR 3.00 (0.67 to 13.46)	50 (1 study)	⊕⊖⊖⊖ **very low**[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **NR:** not reported; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels for risk of bias (randomisation and blinding, double downgrade) and imprecision.

BACKGROUND

Description of the condition

Pilonidal sinus disease is a common condition and mainly affects young adults. The term pilonidal derives from the Latin words for hair (pilus) and nest (nidus) and was first described by Mayo in 1833 (Mayo 1833). Pilonidal sinus is an acquired disease, which results in obstruction of hair follicles in the natal cleft (the anatomical groove between the buttocks), a commonly affected area. Subsequent rupture of the follicles leads to abscess and sinus formation. This condition is further exacerbated by ingrown loose hairs into these sinuses (Hull 2002; Karydakis 1992). In one Norwegian study, the estimated incidence of pilonidal sinus was 26 per 100,000 of the population (Søndenaa 1995). The mean age at consultation is 29 years in men and 25 years in women. Risk factors for development of the condition include male gender, extensive body hair, young adulthood, family history, local trauma, sedentary lifestyle, poor hygiene, an anatomically deep natal cleft and obesity (Akinci 1999; Søndenaa 1995; Thompson 2010). Apart from the health considerations, there is also an economic implication for healthcare systems and society in managing this condition.

The ideal management of pilonidal sinus disease should be simple, cost-effective, easy to perform and lead to a rapid return to normal activities, with low rates of infection and recurrence, and rapid wound healing. Acute presentation with pilonidal abscess is treated with simple incision and drainage. However, one patient in five will experience recurrent symptoms (Jensen 1988). Chronic pilonidal sinus disease presents as recurrent episodes of infection, pain and discharge from the natal cleft. There is no consensus as yet on the management of pilonidal sinus disease, but all interventions are surgical and are split, in broad terms, into two strategies: excision without closure to allow healing through secondary intention (wound left open) or excision with primary closure (wound closed at the time of surgery). A Cochrane Review in 2010 showed that healing through secondary intention had lower recurrence rates compared with primary closure (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.46 to 0.93) but at the expense of longer healing times (41 to 120 days in healing through secondary intention versus 10 to 27 days in primary closure) (Al-Khamis 2010). For people who undergo primary closure there is a clear benefit in terms of rates of recurrence if it is performed through off-midline closure (wound lying adjacent to the natal cleft) versus midline closure (wound lying within the natal cleft) (Enriquez-Navascues 2014). Commonly performed off-midline closure techniques include the Karydakis flap, Bascom II technique, and Rhomboid and Limberg flaps; however, the results are variable. Although these flap techniques have low recurrence and infection rates, they may lead to complications and significantly delayed return to employment (Thompson 2010).

Description of the intervention

Fibrin glue may offer an alternative to surgery in the definitive treatment of pilonidal sinus disease. The glue has been used for a variety of applications over the last 15 years (Spotnitz 2010), including anal fistulas (Sentovich 2003), skin grafts (Currie 2001), and haemostasis (an intervention that stops the bleeding process) (Rutgeerts 1997). Treatment costs are dependent on volume and brand although treatment costs are typically low (approximately GBP 200 per treatment). The fibrin glue is composed of fibrinogen and thrombin, causing formation of a fibrin clot within the sinus. Studies suggest few complications (0% to 12.5%), low recurrence rates (0% to 17%) (Handmer 2012), early return to normal activities (Lund 2005; Patti 2006), and high levels of patient satisfaction (Elsey 2013). However, these are often small observational studies and therefore conclusions are limited. Complications may include seromas and wound breakdown (Handmer 2012). Many previous studies have used fibrin glue as an adjunct to surgical treatment, for example, to close dead space (a cavity remaining after closure of a wound) in primary closure techniques. However, fibrin glue as monotherapy may be an alternative intervention to surgery for pilonidal sinus disease.

How the intervention might work

Thrombin within the glue mixture converts fibrinogen to fibrin, forming a fibrin clot within the sinus. Both thrombin and fibrin are normal blood products produced during the blood clotting process. This may reduce dead space within the sinus and promote healing without the need for invasive surgical excision and associated wound-healing complications, and thus allow a faster return to normal activities.

Why it is important to do this review

Consensus on the optimal treatment for pilonidal sinus disease is lacking. There are a wide variety of techniques, each with advantages and disadvantages. As found in a previous Cochrane review, more invasive procedures lead to less recurrence at the expense of delayed recovery time and slower healing (Al-Khamis 2010). Therefore, no current treatment satisfies the criteria for an ideal therapy for pilonidal sinus disease. Fibrin glue is a less invasive, novel monotherapy that has shown promise in observational studies. However, evidence from randomised controlled trials is required, as this is the optimum method to assess the effects of this intervention. Previous systematic reviews have included both observational studies and randomised controlled trials and no data from unpublished studies (Handmer 2012; Kayaalp 2016). Therefore, a rigorous summary of the evidence is required to determine whether fibrin glue should be more widely used for treating pilonidal sinus disease.

OBJECTIVES

To assess the effects of fibrin glue alone or in combination with surgery compared with surgery alone in the treatment of pilonidal sinus disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) only.

Types of participants

We included all ages of participants in the review. There was no restriction on the setting in which the treatment was delivered. We considered studies including both new and recurrent pilonidal sinus.

Types of interventions

Fibrin glue (any brand containing a mixture of fibrinogen and thrombin, human or bovine) compared with other surgical

techniques such as primary closure, closure through secondary intention and off-midline closure techniques. We also included trials if they used fibrin glue as an adjunct to surgery (compared with surgery alone).

Types of outcome measures

Primary outcomes

- Healing (time to wound healing in days)
- Adverse events (seroma and allergic reaction).

Secondary outcomes

- Infection - surgical site infection (SSI) (proportion of pilonidal sinus surgical sites infected during follow-up as reported in the study)
- Recurrence - of treated pilonidal sinus as opposed to a new pilonidal sinus at another site (proportion of treated pilonidal sinus that recurred during follow-up as reported in the study)
- Postoperative or post-procedural pain (measured using a validated scale such as a visual analogue scale (VAS))
- Time to return to normal activities (days)
- Quality of life (measured using validated scales such as SF-36, EQ-5D or the Cardiff Wound Impact Schedule)
- Cost difference (of treatment, postoperative care and loss of employment in GBP or USD)
- Length of stay in hospital (days).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases to identify relevant RCTs:

- the Cochrane Wounds Specialised Register (searched 13 December 2016);
- The Cochrane Central Register of Controlled Trials (CENTRAL; 2016, issue 12) in the Cochrane Library;
- Ovid MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily) (1946 to 13 December 2016);
- Ovid Embase (1974 to 13 December 2016);
- EBSCO CINAHL Plus (1937 to 13 December 2016).

The search strategies for CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus can be found in Appendix 1. We did not combine the topic-specific searches with any RCT filters as the number of search results were low. There were no restrictions with respect to language, date of publication or study setting.

We also searched the following clinical trials registries (searched December 2016):

- ClinicalTrials.gov;
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)
- EU Clinical Trials Register.

Searching other resources

There was no language restriction in the search and, where necessary, we translated non-English language papers using Google Translate. We sought grey literature from OpenSIGLE. We searched conference proceedings from the last three years (Association of Coloproctology of Great Britain and Ireland, European Society of Coloproctology, Royal Society of Medicine Coloproctology Section and American Society of Colon and Rectal Surgeons). We handsearched reference lists of identified studies for other suitable papers. We utilised Google Scholar to identify papers that had cited identified studies.

Data collection and analysis

We conducted data analysis using Review Manager 5 (RevMan 5) (RevMan 2014) according to methods stipulated in the published review protocol (Lund 2015).

Selection of studies

Two review authors independently matched studies to the inclusion and exclusion criteria (BD and JPW) and, if any disagreement existed, a third review author was consulted and we reached agreement by consensus. We extracted the titles and abstracts of potentially relevant studies onto an electronic database and these underwent full-text review with duplicates being removed. We used full-text reports to match against the inclusion and exclusion criteria. We used the kappa statistic to measure agreement during the selection process. We identified duplicate publications of the same studies by using author names, study location, intervention details and cohort dates. We planned to link any duplicate publications. As one review author had authored one of the included studies (JL), we performed selection of studies using two different authors to reduce bias.

Data extraction and management

Two review authors independently collected and extracted data into an electronic database (BD and ST). As one review author had authored one of the included studies, we performed data extraction using two different authors to reduce bias. We then compared the data and resolved discrepancies by checking the original study. We stored data on a password-protected computer. If any information was not reported, we contacted the study authors for further information.

Where possible we extracted the following data:

- bibliographic data including date of completion/publication;
- country of origin;
- publication status of study;
- source of funding for trial;
- trial design;
- care setting;
- number of participants randomised to each trial arm and number included in final analysis;
- eligibility criteria and key baseline participant data including category(s) and location(s) of sinus;
- details of treatment regimen received by each group;
- duration of treatment;
- details of any co-interventions;
- primary and secondary outcome(s) (with definitions and, where applicable, time points);
- outcome data for primary and secondary outcomes (by group);
- duration of follow-up;

- number of withdrawals (by group) and number of withdrawals (by group) due to adverse events;
- adverse events.

Assessment of risk of bias in included studies

Two study authors (BD and ST) assessed risk of bias independently and a third author resolved any disagreements (JPW). We used the Cochrane tool for assessing risk of bias (Appendix 2; Higgins 2011a). We recorded sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. We assigned each study low, high or unclear risk of bias using published criteria (Higgins 2011a). To assess selective outcome reporting, we searched clinical trials databases for the original study registration and compared this with the published study. In terms of blinding, we recognised that this would be difficult to implement fully as in other surgical studies. However, blinding of outcome assessment was deemed possible in studies comparing fibrin glue as an adjunct to surgery. We presented risk of bias data in a summary table and 'Risk of bias' graph.

Measures of treatment effect

We presented dichotomous outcomes as risk ratios (RR). We presented continuous outcomes as mean differences (MD) if scales were comparable or standardised mean differences (SMD) if non-comparable scales were used. We would have reported time-to-event data as hazard ratios (HR). If HR were not reported, we would have estimated these using the events in each group and derived the P value from the log rank test (Tierney 2007). Where time to healing was wrongly reported as a continuous outcome (as opposed to a time-to-event outcome) and we were not able to derive hazard ratios we endeavoured to find out whether all participants had healed and we planned to exclude such data from meta-analyses.

Unit of analysis issues

As the person was the unit of analysis and they are likely to have only one pilonidal sinus, there were no unit of analysis issues (Higgins 2011b).

Dealing with missing data

If studies with missing data were identified, we contacted the study authors. If we received no response, we extracted data from published graphs if appropriate. If standard deviations were not reported, we estimated these from other studies in the review. We used the most clinically similar study to the one with missing values for these estimates. We did not use methods of imputation for missing participant data.

Assessment of heterogeneity

We assessed clinical heterogeneity during the data extraction process, especially the trial methods and baseline demographics. If significant clinical heterogeneity was present, we did not pool studies and discussed them in the narrative review. For statistical heterogeneity, we used the I^2 statistic (Higgins 2003). We pooled data using the fixed-effect model in the first instance. If substantial heterogeneity was present, we pooled data using the random-effects model. We used the following cut-off values for the I^2 statistic (Deeks 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We assessed selective reporting bias as part of the Cochrane 'Risk of bias' tool. We planned to assess publication bias qualitatively using funnel plots and quantitatively using Egger's regression test if 10 studies or more were included in the analysis (Sterne 2011). However, the low number of included studies precluded this.

Data synthesis

We presented meta-analysis as forest plots if methods were similar enough that data synthesis was deemed appropriate. If not appropriate, we performed qualitative synthesis. We did not estimate missing data on measures of central tendency from reported values (mean estimated from median). We contacted study authors to provide any missing values. We combined continuous outcomes using generic inverse variance from the standard errors. We combined risk ratios using the Mantel-Haenszel method. We used a fixed-effect model if there was no heterogeneity. If heterogeneity was present, we used the random-effects model (Deeks 2011).

'Summary of findings' table

We have presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE approach, which defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). Evidence from RCTs is downgraded from high quality to moderate, low or very low quality if any of the above uncertainties are present. We have presented the following outcomes in the 'Summary of findings' tables:

- time to healing (days);
- adverse events (seroma and/or allergic reaction).

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis and meta-regression. However, the small number of included studies precluded this.

Sensitivity analysis

We planned to conduct a sensitivity analysis excluding studies that we judged high risk of bias for any of the 'Risk of bias' assessments and those sponsored by pharmaceutical companies. If sensitivity analysis results differed substantially, we would have carefully interpreted the final results.

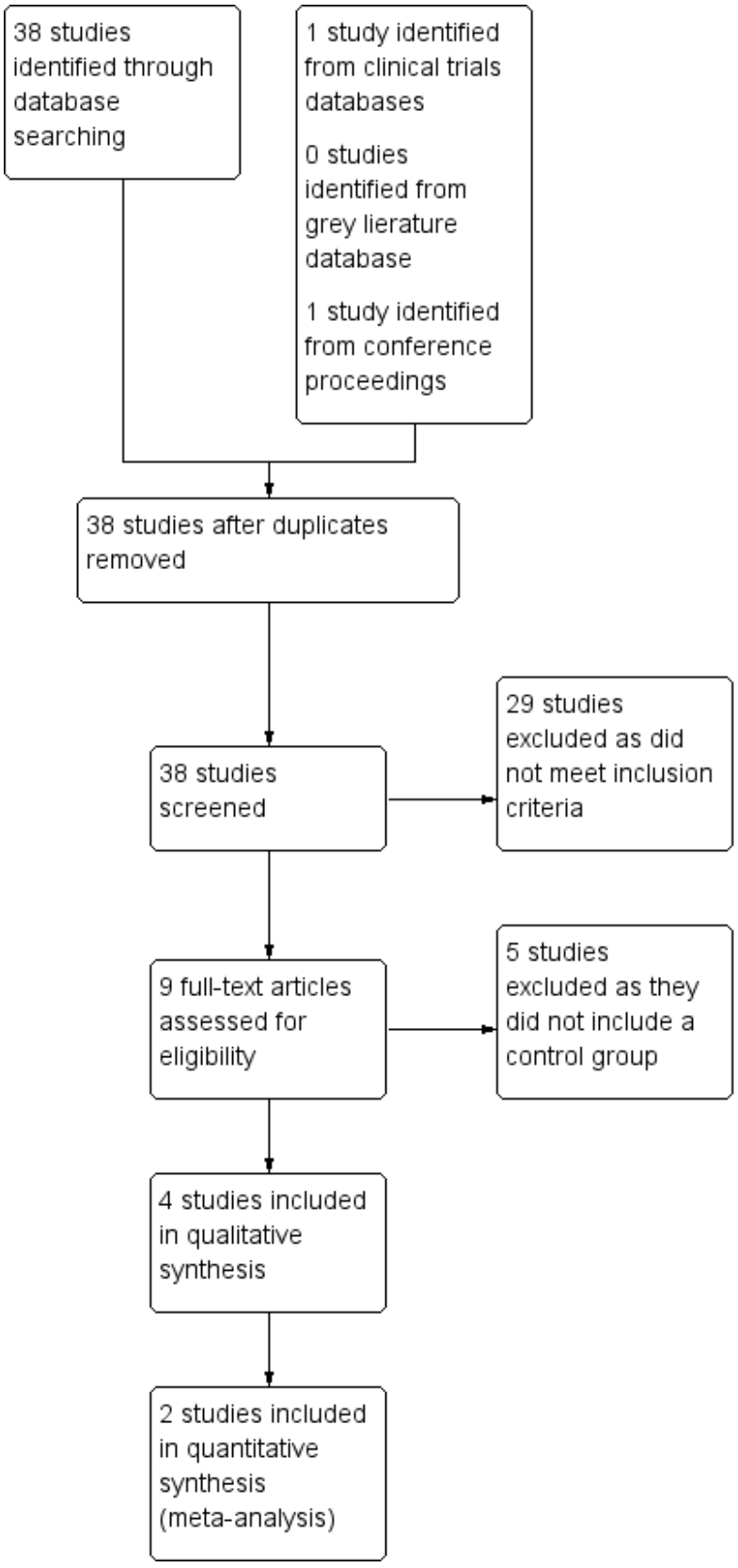
RESULTS

Description of studies

Results of the search

We identified 38 studies from searching of electronic databases (Figure 1) and a further two records from searching clinical trials databases and conference proceedings. However, these were duplicate records from the same study (Lund 2010). Further information was requested and provided from one of the review authors (JL). We considered four studies to be eligible for inclusion in the final review.

Figure 1. Study flow diagram



Included studies

We included four RCTs with 253 participants (Characteristics of included studies; Altinli 2007; Lund 2010; Sözen 2011a; Sözen 2011b). One study was published in abstract form only (Lund 2010). The kappa statistic showed perfect agreement for inclusion of studies when performed in duplicate (κ = 1 by BD and JPW). One study examined fibrin glue compared with Bascom's procedure (Lund 2010), two studies examined fibrin glue as an adjunct to Limberg flap (Altinli 2007; Sözen 2011b) and one study examined fibrin glue as an adjunct to Karydakis flap (Sözen 2011a). The interventions used were 1 ml to 2 ml of Tisseel fibrin glue in one study (Lund 2010) and 6 ml of Cryoseal FS System fibrin glue in three studies (Altinli 2007; Sözen 2011a; Sözen 2011b). In two of the studies, only the control group received postoperative drains (Sözen 2011a; Sözen 2011b). All studies were conducted in adults and three studies included men only (Altinli 2007; Sözen 2011a; Sözen 2011b). All studies were conducted in a secondary care setting. One study was conducted in the UK (Lund 2010) and three studies were conducted in Turkey (Altinli 2007; Sözen 2011a; Sözen 2011b). None of the included studies reported sources of funding. The number of participants in the studies were 32 (Altinli 2007), 39 (Lund 2010), 50 (Sözen 2011a) and 132 (Sözen 2011b).

One study reported the following outcomes: drainage volume, length of stay, proportion of wounds infected, seroma (adverse event) and mortality (Altinli 2007). One unpublished study reported: pain, quality-of-life scores, analgesia usage, recurrence, infection, time to return to normal mobility and employment and cost reduction compared with surgery (Lund 2010). One study reported: length of stay, seroma and recurrence (Sözen 2011a). The final study reported: postoperative pain, time to first mobilisation, length of stay, time to return to employment, infection, flap oedema, wound dehiscence, seroma, healing time and duration of surgery (Sözen 2011b). Units of measurement can be found in the characteristics of included studies tables (Characteristics of included studies). Follow-up in the included studies were: mean 8.5 months and 8.2 months (intervention and control group respectively) (Altinli 2007), median 4.6 years (Lund 2010), median 10.2 months (Sözen 2011a) and mean 2 months and 6 months (intervention and control group respectively) (Sözen 2011b). The methods of outcome assessment were not reported in one study (Altinli 2007). One study reported that a questionnaire was used to assess duration of recovery and that participants were followed up weekly until wounds had healed then every three months for one year (Sözen 2011b). One study followed up participants with physical examination at one month then six monthly thereafter (Sözen 2011a). One study measured outcomes at one and six weeks in clinic (Lund 2010). Due to the differences between the Karydakis and Limberg procedures, we did not pool data from these different surgical approaches together. The Karydakis procedure involves an off-midline elliptical incision, whilst the Limberg procedure involves a rhomboid incision with a flap constructed from an additional lateral incision. Moreover, previous research has shown differing outcomes for these surgical techniques making separate comparisons more clinically appropriate (Bali 2015).

Excluded studies

We excluded five studies that were not RCTs (Characteristics of excluded studies; Greenberg 2004; Isik 2014; Lund 2005; Patti 2006; Seleem 2005).

Risk of bias in included studies

We performed 'Risk of bias' assessments using the Cochrane tool for assessing risk of bias (Higgins 2011a). We regarded all the included studies as being at high risk of bias. The assessments for each study can found in Figure 2 and Figure 3. Details on the criteria for assessing risk of bias can be found in Appendix 2.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

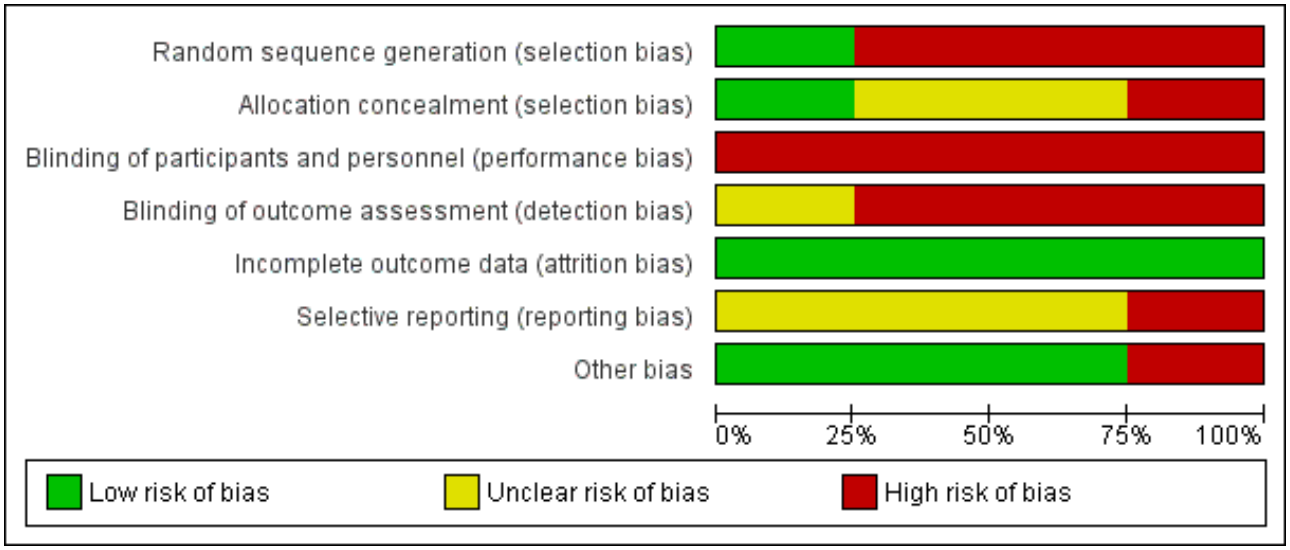
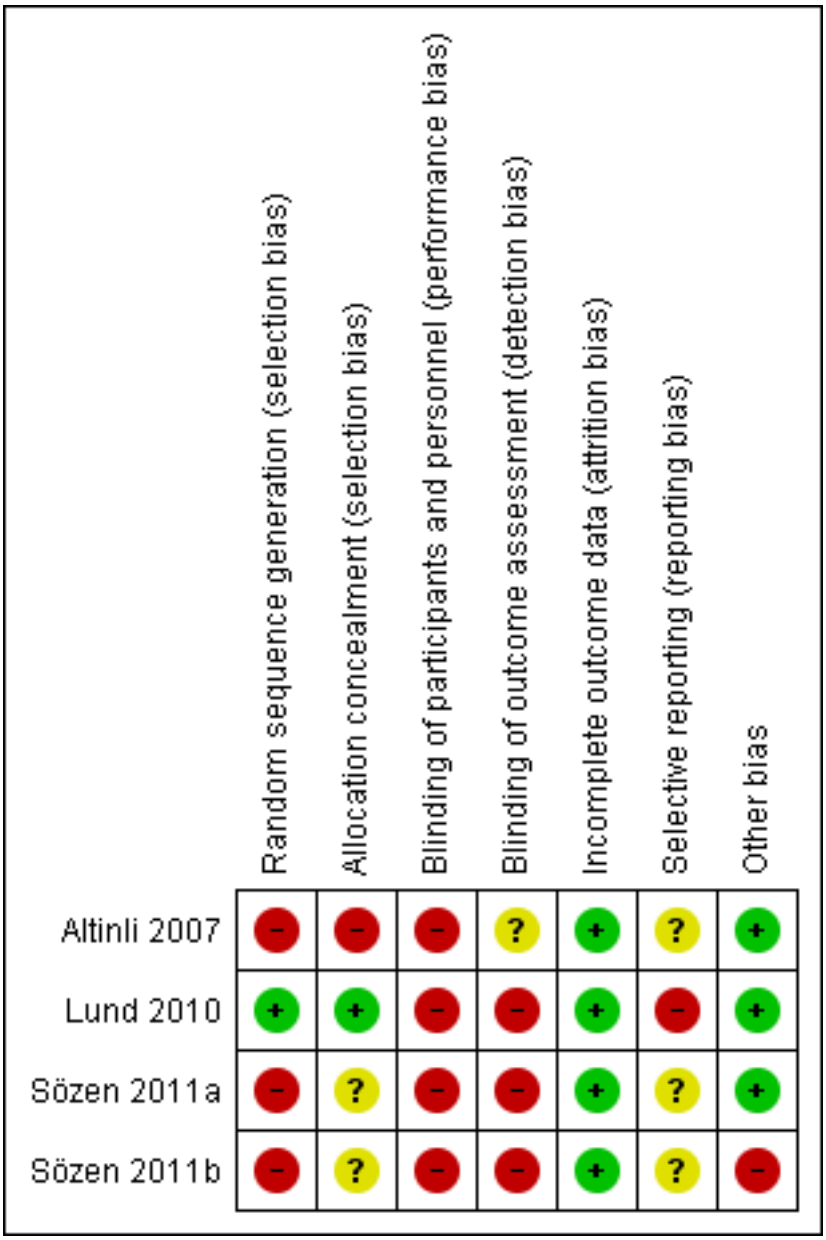


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Two studies randomised participants on the basis of an admission protocol number and therefore were classified at high risk of bias for randomisation and unclear risk for allocation concealment, as there was not enough information to determine whether allocation of participants from this protocol number could be foreseen (Sözen 2011a; Sözen 2011b). One study randomised participants on the basis of the day they were first seen in clinic and therefore we regarded it as being at high risk of bias for both randomisation and allocation concealment (Altinli 2007). One study used computer-generated randomisation and allocated participants using sequentially-numbered, sealed opaque envelopes and therefore was assessed as low risk for both domains (Lund 2010).

Blinding

None of the included studies used a placebo substitute for fibrin glue. Two studies used postoperative drains in the control group but not the fibrin glue group and were therefore regarded as high risk for performance and detection bias (Sözen 2011a; Sözen 2011b). One study did not have differential use of postoperative drains although the care-giver was not blinded so we regarded at high risk for performance bias and unclear risk for detection bias, as no details were provided on outcome assessment (Altinli 2007). One study used fibrin glue monotherapy compared with surgery (Bascom's procedure) and therefore could not be blinded, so we classified it at high risk for performance and detection bias (Lund 2010).

Incomplete outcome data

Three studies did not report any participants lost to follow-up and therefore we regarded them to be at low risk of bias for this domain (Altinli 2007; Sözen 2011a; Sözen 2011b). One study lost one participant to follow-up in the control group; this study was classified as low risk, as it was not thought this would significantly bias the results obtained (Lund 2010).

Selective reporting

Only one study registered on a clinical trials database and healing was pre-stated on registration although not reported in a published abstract so we regarded this as high risk of bias (Lund 2010). We could not identify any published clinical trials registration for the three other studies and we regarded all these as being at unclear risk of bias for this domain (Altinli 2007; Sözen 2011a; Sözen 2011b).

Other potential sources of bias

Three studies had similar baseline characteristics and no other risks of bias and therefore we classified them at low risk for this domain (Altinli 2007; Lund 2010; Sözen 2011a). One study had different lengths of follow-up in the fibrin and control groups (mean follow-up two months and six months respectively) and therefore was classified at high risk for this domain (Sözen 2011b).

Effects of interventions

See: **Summary of findings for the main comparison** Fibrin glue compared with Bascom's procedure for pilonidal sinus; **Summary of findings 2** Limberg flap plus fibrin glue compared with Limberg flap for pilonidal sinus; **Summary of findings 3** Karydakis flap plus fibrin glue compared with Karydakis flap and drain for pilonidal sinus

Fibrin glue versus Bascom's procedure (one RCT, 39 participants)

Primary outcomes

Healing

This outcome was not reported in the included study. Further data showed that all wounds had healed at follow-up (median 11 months) although there were no data to calculate time to healing.

Adverse events

These outcomes were not reported in the included study.

Secondary outcomes

Infection

We included one unpublished study with 39 participants in this outcome (Lund 2010). It is uncertain whether there was a difference in infection rates at a median follow-up of 11 months with fibrin glue when compared with Bascom's procedure (RR 0.57, 95% CI 0.16 to 2.06) (Analysis 1.1). The quality of evidence was very low-quality according to GRADE (downgraded twice for risk of bias and for imprecision).

Recurrence

The same unpublished study (39 participants) reported this outcome (Lund 2010). It is uncertain whether there was a difference in the proportion of participants suffering a recurrence of their pilonidal sinus within a median follow-up period of 11 months (RR 0.95, 95% CI 0.06 to 14.13). The quality of evidence was very low (downgraded twice for risk of bias and for imprecision). It is also uncertain whether there was a difference on longer-term follow-up (median 4.6 years) in the same study (Lund 2010) (RR 1.43, 95% CI 0.27 to 7.61) (Analysis 1.2; very low-quality evidence downgraded twice for risk of bias and for imprecision).

Pain

The same unpublished study (39 participants) reported this outcome (Lund 2010). This study measured pain on an 11-point scale, from day one to day seven after the procedure however we report results from day one as this a standard time to measure pain in trials of postoperative analgesics. Fibrin glue may reduce pain on day one after the procedure (MD -2.50, 95% CI -4.03 to -0.97) (Analysis 1.3), measured on an 11-point scale. The quality of evidence was low (downgraded twice for risk of bias).

Time to return to normal activities

The same unpublished study (39 participants) reported this outcome (Lund 2010). Fibrin glue may reduce the time to return to employment compared with Bascom's procedure (MD -34.80 days, 95% CI -66.82 days to -2.78 days) (Analysis 1.4), however this finding is highly uncertain. The quality of evidence was very low (downgraded twice for risk of bias and for imprecision).

Quality of life

The same unpublished study (39 participants) reported this outcome (Lund 2010). It is uncertain whether fibrin glue leads to an improvement in quality of life at day seven, measured using the EQ-5D scale (MD 8.00, 95% CI -0.10 to 16.10) (Analysis 1.5). The quality of evidence was very low (downgraded twice for risk of bias and for imprecision).

Cost difference

The same unpublished study (39 participants) reported this outcome (Lund 2010). Non-reporting of standard deviations or costs in each group precluded inclusion in the analysis. The study reported a cost reduction of GBP 1120 (USD 1623) in the fibrin glue participants compared with participants in the Bascom's procedure group.

Length of stay

This outcome was not reported in the included study.

Limberg flap with and without fibrin glue (two RCTs, 164 participants)

Primary outcomes

Healing

One study (132 participants) reported this outcome (Sözen 2011b) as time to healing, albeit wrongly regarding time to healing as a continuous outcome. We were able to discern from the published data that all participants healed and therefore all contributed data to the analysis. Fibrin glue as an adjunct to Limberg flap may decrease the time to healing compared with Limberg flap with a suction drain (MD -13.95 days, 95% CI -16.76 days to -11.14 days) (Analysis 2.1) however this is highly uncertain. The quality of evidence was very low (downgraded twice for risk of selection, performance and detection bias and imprecision).

Adverse events

Two studies with 164 participants reported this outcome and they were pooled using a fixed-effect model (I^2 = 0%) (Altinli 2007; Sözen 2011b). It is uncertain whether using fibrin glue alongside the Limberg flap affected the incidence of seroma (RR 0.27, 95% CI 0.05 to 1.61) (Analysis 2.2). The quality of evidence was very low (downgraded twice for risk of selection, performance and detection bias and for imprecision). The incidence of allergic reactions was not reported in either study.

Secondary outcomes

Infection

The same two studies with 164 participants reported this outcome and their results were pooled using a fixed-effect model (I^2 = 0%) (Altinli 2007; Sözen 2011b). It is uncertain whether using glue alongside the Limberg flap affected the incidence of postoperative infection (RR 0.33, 95% CI 0.04 to 3.11) (Analysis 2.3). The quality of the evidence was very low (downgraded twice for risk of selection, performance and detection bias and for imprecision).

Recurrence

One study with 132 participants reported this outcome (Sözen 2011b) and found no cases of recurrence in either group.

Postoperative pain

The same study involving 132 participants reported this outcome (Sözen 2011b). Fibrin glue as an adjunct to the Limberg flap may decrease postoperative pain (measured on a 10 cm VAS on day one) compared with the Limberg flap and a suction drain (median score with glue as an adjunct was 2, median score without glue was 4; reported P < 0.001). The quality of evidence was low (downgraded twice for risk of selection, performance and detection bias).

Time to return to normal activities

The same study involving 132 participants reported this outcome (Sözen 2011b). Fibrin glue as an adjunct to Limberg flap may decrease the time taken to return to normal activities compared with Limberg flap and suction drain (median time with glue was 8 days versus 17 days without glue; reported P < 0.001). The quality of evidence was low (downgraded twice for risk of selection, performance and detection bias).

Quality of life

This outcome was not reported in either study.

Cost difference

This outcome was not reported in either study.

Length of stay

Two studies involving 164 participants reported this outcome and results were pooled using a random-effects model (I^2 = 79%) (Altinli 2007; Sözen 2011b). It is unclear whether using fibrin glue with the Limberg flap reduced length of hospital stay compared with the Limberg flap alone (MD -1.69 days, 95% CI -2.08 days to -1.29 days) (Analysis 2.4). The quality of evidence was very low (downgraded for unexplained heterogeneity and twice for risk of selection, performance and detection bias).

Karydakis flap with and without fibrin glue (one RCT, 50 participants)

Primary outcomes

Healing

This outcome was not reported in the included study (Sözen 2011a).

Adverse events

It is unclear whether using fibrin glue alongside the Karydakis flap affected the incidence of seroma compared with Karydakis flap and postoperative drain (Sözen 2011a) (RR 3.00, 95% CI 0.67 to 13.46) (Analysis 3.1). The quality of evidence was very low (downgraded twice for risk of selection, performance and detection bias and for imprecision). The incidence of allergy was not reported in the included study.

Secondary outcomes

Infection

This outcome was not reported in the included study.

Recurrence

The same study (50 participants) reported this outcome (Sözen 2011a). There was no incidence of recurrence in either group.

Postoperative pain

This outcome was not reported in the included study.

Time to return to normal activities

This outcome was not reported in the included study.

Quality of life

This outcome was not reported in the included study.

Cost difference

This outcome was not reported in the included study.

Length of stay

Fibrin glue used alongside the Karydakis flap may reduce hospital length of stay when compared with Karydakis flap and postoperative drain (Sözen 2011a) (mean length of stay 2 days with glue compared with 3.7 days without glue; reported P < 0.001). The quality of evidence was low (downgraded twice for risk of selection, performance and detection bias).

Sensitivity analysis

We were unable to conduct a sensitivity analysis as all the included studies were at high risk of bias. None of the included studies reported sponsorship by pharmaceutical companies.

Other analyses

We were unable to conduct analyses for publication bias or investigation of heterogeneity due to the low number of included studies.

DISCUSSION

Summary of main results

Our review included four RCTs of fibrin glue (with or without surgery) compared with surgery alone for pilonidal sinus disease (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). One study evaluated fibrin glue as monotherapy compared with Bascom's procedure for people with chronic pilonidal sinus disease (Lund 2010). This study was at high risk of bias for blinding and selective outcome reporting (healing). The study was unpublished and did not report any of our primary outcomes. Although requests for further data showed that all wounds had healed at follow-up, there were no data available with which to calculate time to healing. The study showed that fibrin glue may reduce pain on the first day after the procedure compared with surgery and may reduce time to return to normal activities and costs, however these findings are highly uncertain as the quality of evidence was low or very low. It is highly uncertain whether using glue compared with surgery affected the incidence of infection or recurrence at follow-up.

Two studies evaluated fibrin glue as an adjunct to the Limberg flap compared with the Limberg flap alone in people with chronic pilonidal sinus disease (Altinli 2007; Sözen 2011b). One of these studies also used a suction drain in the group without glue (Sözen 2011b). Both studies were at high risk of bias due to inadequate randomisation and blinding. Very low-quality evidence from one study (Sözen 2011b) suggested fibrin glue as an adjunct to Limberg flap may reduce time to healing but this is very uncertain due to the quality of the evidence (the second study did not report healing). It is unclear whether fibrin glue as an adjunct to the Limberg flap reduced the risk of seroma due to the very low-quality of evidence. Fibrin glue as an adjunct to the Limberg flap may reduce postoperative pain and time to return to normal activities although the quality of evidence was low. It is uncertain whether fibrin glue reduced length of stay when compared with Limberg flap only due to very low-quality of evidence. Furthermore, it is unclear whether fibrin glue affected the incidence of infection or recurrence due to the very low-quality of evidence.

One study evaluated fibrin glue as an adjunct to Karydakis flap compared with Karydakis flap and postoperative drain in people with chronic pilonidal sinus disease (Sözen 2011a). This study was at high risk of bias for randomisation and blinding. This study did not report the primary outcome of time to healing. It is uncertain whether fibrin glue as an adjunct to Karydakis flap affected the incidence of seroma due to the very low-quality of the evidence. There were no incidences of recurrence in either group. Fibrin glue as an adjunct to the Karydakis flap may reduce length of stay although the quality of evidence was low.

Overall completeness and applicability of evidence

During our searches of databases we identified only four RCTs of fibrin glue (with or without surgery) versus surgery. We were able to obtain all the information required from one unpublished study and the only study which evaluated fibrin glue as monotherapy (Lund 2010). However, the pre-stated outcome of healing rate was not reported in the conference abstract. We attempted to contact one author of two of the included studies for further data although we received no response (Sözen 2011a; Sözen 2011b). Therefore, we presented these outcomes as reported within the published report as median with a P value. We are unaware of any other studies that were not included in the review.

In terms of external validity, three of the included studies within the review, which were all conducted in Turkey, evaluated the use of fibrin glue in men only (Altinli 2007; Sözen 2011a; Sözen 2011b). Therefore, it is unclear how the results from these studies apply to women and those from outside this care setting. Although male sex is a risk factor for pilonidal sinus, there is no reason to believe the effects would be different in men and women. In addition, current studies did not include children and therefore the efficacy of fibrin glue in this group is unclear. Furthermore, three studies that evaluated fibrin glue as an adjunct to surgery excluded participants with recurrent disease, which may limit the applicability of the evidence to those with primary disease (Altinli 2007; Sözen 2011a; Sözen 2011b).

Quality of the evidence

For fibrin glue monotherapy, the quality of the evidence was low for pain following the procedure and very low for all other outcomes. For fibrin glue as an adjunct to Limberg flap, the quality of the evidence was low for postoperative pain and time to return to normal activities. However, the quality of evidence was very low for healing, adverse events, infection and length of stay. For fibrin glue as an adjunct to Karydakis flap, the quality of evidence was low for length of stay and very low for adverse events. Severe concerns over risk of bias in all studies evaluating fibrin glue resulted in double downgrading of evidence (Schünemann 2011b).

We were only able to identify four small RCTs (the sample sizes ranged from 39 to 164) and therefore most results are highly imprecise. Two studies were at high risk of selection, performance and detection bias due to the use of randomisation from an admission protocol number and the use of postoperative drains which are highly visible (Sözen 2011a; Sözen 2011b). One of these studies also had differential lengths of follow up (Sözen 2011b). Another study was at high risk of selection bias because participants were allocated based on the day they were seen in clinic although participants were likely blinded to treatment allocation (Altinli 2007). Only one study could be fully assessed for selective outcome reporting as this trial was registered in a clinical trials database, however the pre-specified outcome of healing rate was not reported (Lund 2010). This study was at high risk of bias for performance and detection bias although this would be difficult to address in a trial of surgery compared with a less invasive intervention, which may limit the quality of evidence derived from future studies in this area.

Potential biases in the review process

We used a wide ranging search strategy and were able to retrieve published and most unpublished data from the studies identified. One study author did not reply with further information from two studies (Sözen 2011a; Sözen 2011b), although we were still able to include data qualitatively. One potential bias in the review process was that one of the review authors (JL) was also the author of one of the included studies (Lund 2010). This may have introduced unconscious bias during risk of bias assessments and interpretation of the data from this study. We attempted to mitigate this as far as possible by performing risk of bias assessments in duplicate, not involving this particular review author in these assessments and undergoing thorough peer review to identify any

inappropriate presentation of data or conclusions. Further sources of bias include the estimation of standard deviation values as these may not reflect those from the original data. Furthermore, our decision to input pain data from the first postoperative day may not reflect important differences in pain at other time points.

Agreements and disagreements with other studies or reviews

We are aware of two previous systematic reviews on fibrin glue therapy for chronic pilonidal sinus (Handmer 2012; Kayaalp 2016). However, these reviews included both randomised and observational studies with no data from unpublished studies. In one of these reviews (Handmer 2012), in single group cohort studies, the mean time to return to normal activities was 11 days for fibrin glue (standard deviation 6 days) which is comparable with our results for fibrin glue monotherapy (Lund 2010). These observational studies suggested that the incidence of pilonidal sinus recurrence after fibrin glue was low (1 in 85 patients; average follow-up ranges from 4 to 23 months). We also observed a low incidence of recurrence in participants treated with fibrin glue (1 in 111 patients; average follow-up ranges from 2 to 11 months). Our review differs in only including RCTs which have strengths over single-group cohort studies, which were included in the previous systematic reviews (Handmer 2012; Kayaalp 2016).

AUTHORS' CONCLUSIONS

Implications for practice

At present, the effects of fibrin glue, either as a monotherapy or as an adjunct to surgery, are uncertain due to the quality of the evidence. All the included studies were at risk of bias and included a low number of participants. Low-quality of evidence suggests fibrin glue monotherapy may be associated with less pain than surgery on the first post-procedural day although future research is required to confirm this. We are uncertain about the effects of fibrin glue as an adjunct to the Limberg flap on time to healing and adverse events due to the very low-quality of evidence. Fibrin glue may decrease postoperative pain and time to return to normal activities when used alongside the Limberg flap although the quality of evidence was low. We are uncertain about the effects of fibrin glue as an adjunct to the Karydakis flap on seroma formation; it may reduce length of stay relative to surgery alone however this is highly uncertain due to the low-quality of the evidence. Further, larger and higher quality randomised controlled trials (RCTs) are required to inform clinical practice and patient choice.

Implications for research

Future RCTs should be adequately powered with larger numbers of participants and follow-up, ideally for five years to capture recurrence. Future RCTs should measure and report clinically-important and patient-relevant outcomes such as time to healing, rates of recurrence, infection and pain. Future trials should ensure that robust randomisation and allocation concealment are performed and, wherever possible, blind participants and outcome assessors while ensuring low attrition to follow-up to improve internal validity over the studies published thus far.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Altinli 2007

Methods	Parallel, randomised/quasi-RCT. Conducted in secondary care hospital in Turkey
Participants	Men, participants with recurrent pilonidal sinus excluded. Age (mean 24.5 years (fibrin glue) and 22.5 years (control)); BMI (mean 25.7 (fibrin glue) and 25.3 (control)). 32 participants enrolled

Altinli 2007 *(Continued)*

Interventions	Intervention (16 participants with mean follow-up of 8.5 months): Limberg flap and 6 ml of fibrin glue (Cryoseal FS System) Control (16 participants with mean follow-up of 8.2 months): Limberg flap
Outcomes	Drainage volume (ml) Length of stay (days) Infection (%) Seroma (%) Mortality (%)
Notes	Participants with purulent discharge had 1 week of antibiotics prior to procedure. All procedures performed under spinal anaesthesia. All participants had postoperative drains. No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomised into 2 groups, according to the day the participant was first seen in the clinic (odd and even days)
Allocation concealment (selection bias)	High risk	Participants were randomised into 2 groups, according to the day the participant was first seen in the clinic (odd and even days)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants unlikely to know whether they received the intervention. However, it would not have been possible to blind the care giver
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No mention of outcomes in methods or reference to published protocol
Other bias	Low risk	Although limited, similar baseline groups. No mention of sources of funding or conflicts of interest

Lund 2010

Methods	Parallel, RCT. Unpublished (although abstract previously published). Secondary care hospital in the UK
Participants	Participants excluded if prior allergy to fibrin glue, women not taking contraceptives, unable to give informed consent, objection to product on moral or religious grounds. Age (median 29 years (fibrin glue) and 31 years (surgery)); men (50% (fibrin glue) and 47.3% (surgery)). 40 participants enrolled
Interventions	Intervention (20 participants): fibrin glue (TISSEEL glue)

Lund 2010 *(Continued)*

	Control (20 participants; 19 analysed due to 1 participant lost to follow-up): Bascom's procedure
Outcomes	Pain (11-point scale on the first 7 days) Quality of life scores (EQ-5D) Analgesia usage (assigned points per day, 1 point for simple analgesia and 2 points for opioid analgesia) Recurrence (%; defined as return of symptoms) Infection (%; clinical infection requiring treatment) Time to return to normal mobility and employment (days) Cost reduction (GBP). We included pain score data from day one only as this is the standard time of reporting for postoperative pain trials. Analgesic usage was measured in this study but we did not report this as this was not one of our *a priori* outcomes for the review. Outcomes assessed in clinic at one and six weeks.
Notes	Same surgeon operated on participants. All procedures performed under general anaesthetic. Study author provided further information. No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Participants were informed by opening of sequentially-numbered, sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding. Data collected by member of the surgical team
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one participant in control group lost to follow-up
Selective reporting (reporting bias)	High risk	Outcomes stated in original protocol (ISRCTN56652573). Healing not reported in abstract
Other bias	Low risk	Same surgeon operated on participants. Similar baseline characteristics

Sözen 2011a

Methods	Parallel, RCT/quasi-randomised trial. Secondary care hospital in Turkey

Sözen 2011a *(Continued)*

Participants	Men with pilonidal disease. Participants were excluded if they had concurrent abscess, recurrent pilonidal disease or tracts extending more than 3 cm laterally. Age (mean 22.5 years (fibrin glue) and 24 years (control)); BMI (mean 26 (fibrin glue) and 25.75 (control)). 50 participants enrolled
Interventions	Intervention (25 participants): Karydakis flap and 6 ml fibrin glue (CryoSeal FS System) Control (25 participants); Karydakis flap and drain. Median follow-up 10.2 months for both groups
Outcomes	Length of stay (days) Seroma (%) Recurrence (%)
Notes	Drains in situ for a median of 3 days. No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The participants were randomised into 2 groups—drained and fibrin sealant—according to the admission protocol number. Details of this protocol number unclear
Allocation concealment (selection bias)	Unclear risk	The participants were randomised into two groups—drained and fibrin sealant—according to the admission protocol number. Details of this protocol number unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used. One group had drain
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention. One group had drain
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline groups

Sözen 2011b

Methods	Parallel, RCT/quasi-randomised trial. Secondary care hospital in Turkey
Participants	Men with pilonidal sinus. Participants were excluded if recurrent disease, large cavity or if sinus extended lateral to natal cleft or orifice near anus. Age (mean 23.5 years (fibrin glue) and 25 years (control)); BMI (mean 26 (fibrin glue) and 25.75 (control)). 132 participants enrolled

Sözen 2011b *(Continued)*

Interventions	Intervention (66 participants with mean follow-up of 2 months): Limberg flap plus 6 ml fibrin glue (CryoSeal FS System) Control (66 participants with a mean follow-up of 6 months): Limberg flap and suction drain
Outcomes	Postoperative pain (10 cm VAS score) Time to first mobilisation Length of stay (days) Time to return to employment (time from day of surgery to day returned to work or leisure activities) Infection (%) Flap oedema (%) Wound dehiscence (%) Seroma (%) Healing time (days) Duration of surgery (first incision to last suture)
Notes	All procedures performed under spinal anaesthesia. No funding source reported. All participants followed up weekly until wound healing

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The participants were randomised into two groups, drained and non-drained, according to the admission protocol number. Nature of this protocol number unclear
Allocation concealment (selection bias)	Unclear risk	The participants were randomised into two groups, drained and non-drained, according to the admission protocol number. Nature of this protocol number unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Control group had drain
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention. Control group had drain
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	High risk	Different lengths of follow-up

BMI: body mass index
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Greenberg 2004	No control group
Isik 2014	No control group
Lund 2005	No control group
Patti 2006	No control group
Seleem 2005	No control group

DATA AND ANALYSES

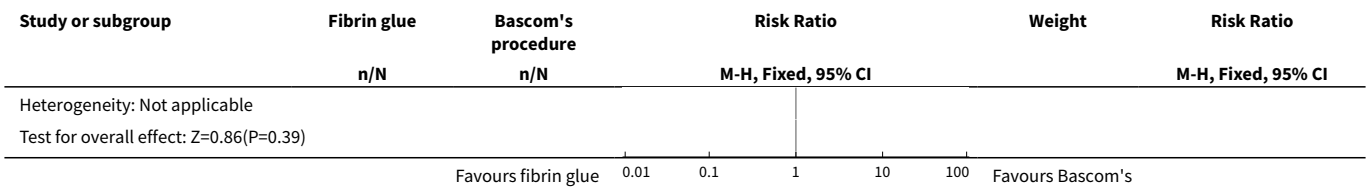
Comparison 1. Fibrin glue versus Bascom's procedure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.16, 2.06]
2 Recurrence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Median 11 months' follow-up	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.06, 14.13]
2.2 Median 4.6 years' follow-up	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.27, 7.61]
3 Pain (Day 1)	1	39	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-4.03, -0.97]
4 Time to return to normal activities (days)	1	39	Mean Difference (IV, Fixed, 95% CI)	-34.8 [-66.82, -2.78]
5 Quality of life (EQ-5D at Day 7)	1	39	Mean Difference (IV, Fixed, 95% CI)	8.0 [-0.10, 16.10]

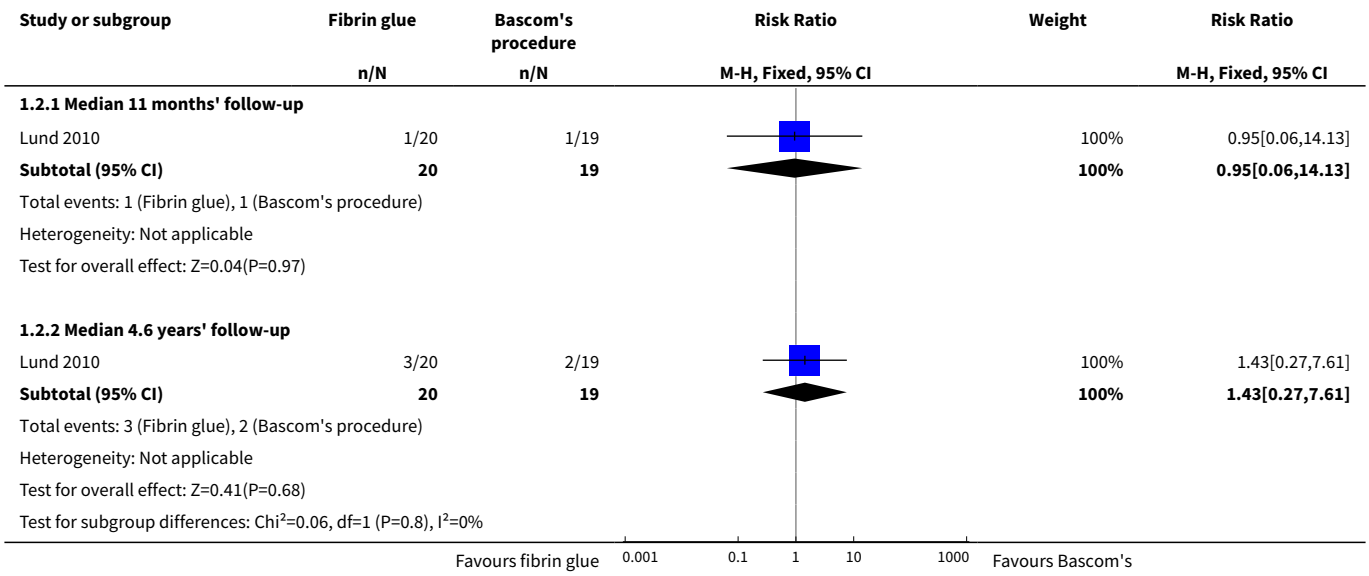
Analysis 1.1. Comparison 1 Fibrin glue versus Bascom's procedure, Outcome 1 Infection.

Study or subgroup	Fibrin glue n/N	Bascom's procedure n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Lund 2010	3/20	5/19		100%	0.57[0.16,2.06]
Total (95% CI)	**20**	**19**		**100%**	**0.57[0.16,2.06]**
Total events: 3 (Fibrin glue), 5 (Bascom's procedure)					

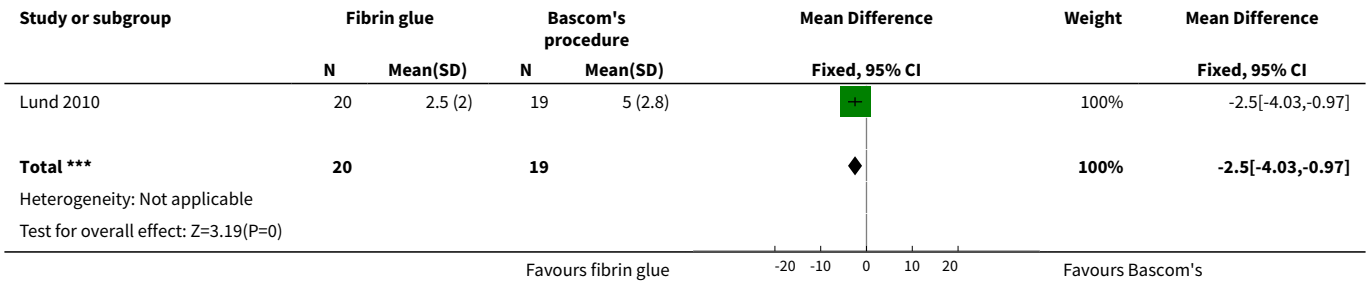
Favours fibrin glue — Favours Bascom's



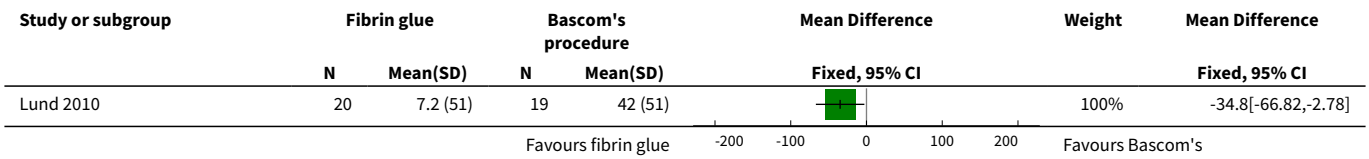
Analysis 1.2. Comparison 1 Fibrin glue versus Bascom's procedure, Outcome 2 Recurrence.

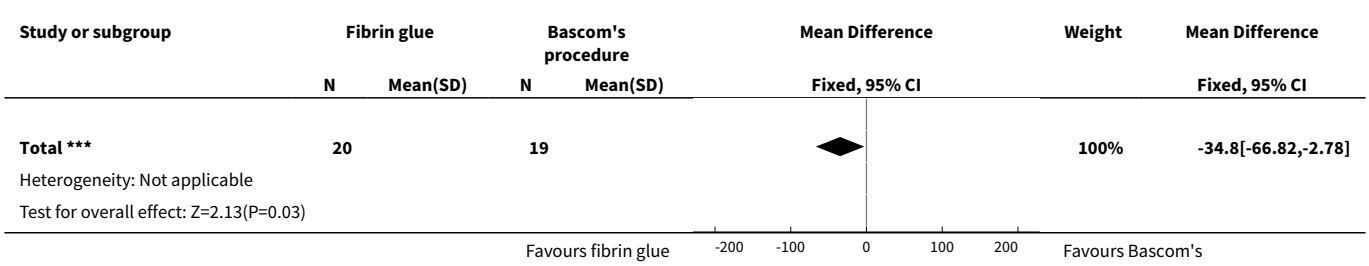


Analysis 1.3. Comparison 1 Fibrin glue versus Bascom's procedure, Outcome 3 Pain (Day 1).

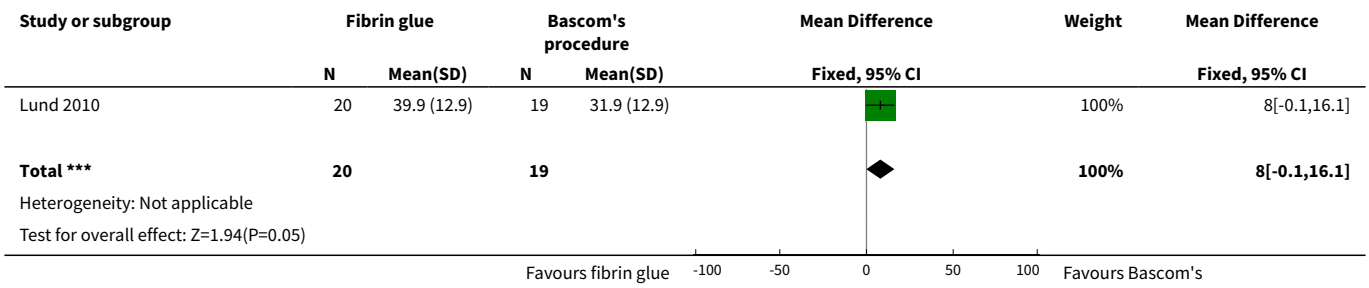


Analysis 1.4. Comparison 1 Fibrin glue versus Bascom's procedure, Outcome 4 Time to return to normal activities (days).





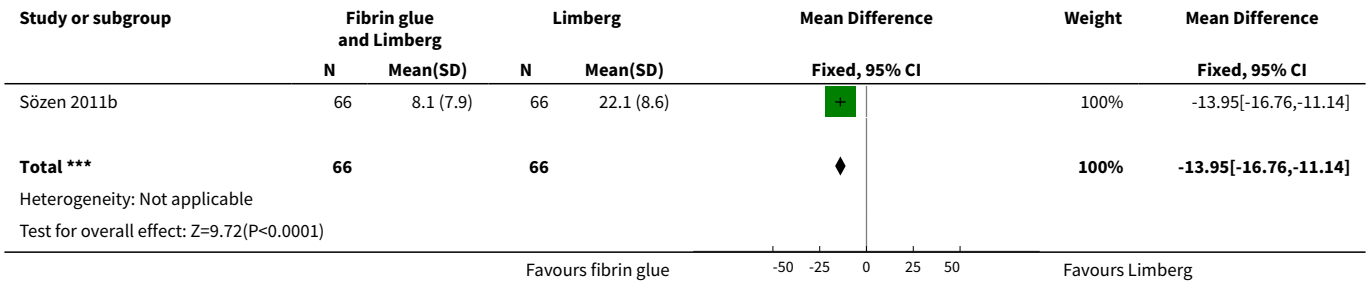
Analysis 1.5. Comparison 1 Fibrin glue versus Bascom's procedure, Outcome 5 Quality of life (EQ-5D at Day 7).



Comparison 2. Fibrin glue and Limberg flap versus Limberg flap

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing (days)	1	132	Mean Difference (IV, Fixed, 95% CI)	-13.95 [-16.76, -11.14]
2 Adverse event (seroma)	2	164	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.05, 1.61]
3 Infection	2	164	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.11]
4 Length of stay (days)	2	164	Mean Difference (IV, Random, 95% CI)	-1.69 [-2.08, -1.29]

Analysis 2.1. Comparison 2 Fibrin glue and Limberg flap versus Limberg flap, Outcome 1 Healing (days).



Analysis 2.2. Comparison 2 Fibrin glue and Limberg flap versus Limberg flap, Outcome 2 Adverse event (seroma).

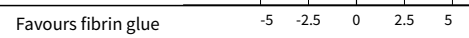
Study or subgroup	Fibrin glue and Limberg n/N	Limberg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Altinli 2007	0/16	1/16		27.27%	0.33[0.01,7.62]
Sözen 2011b	1/66	4/66		72.73%	0.25[0.03,2.18]
Total (95% CI)	**82**	**82**		**100%**	**0.27[0.05,1.61]**
Total events: 1 (Fibrin glue and Limberg), 5 (Limberg)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=1.43(P=0.15)					

Analysis 2.3. Comparison 2 Fibrin glue and Limberg flap versus Limberg flap, Outcome 3 Infection.

Study or subgroup	Fibrin glue and Limberg n/N	Limberg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Altinli 2007	0/16	1/16		50%	0.33[0.01,7.62]
Sözen 2011b	0/66	1/66		50%	0.33[0.01,8.04]
Total (95% CI)	**82**	**82**		**100%**	**0.33[0.04,3.11]**
Total events: 0 (Fibrin glue and Limberg), 2 (Limberg)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.96(P=0.33)					

Analysis 2.4. Comparison 2 Fibrin glue and Limberg flap versus Limberg flap, Outcome 4 Length of stay (days).

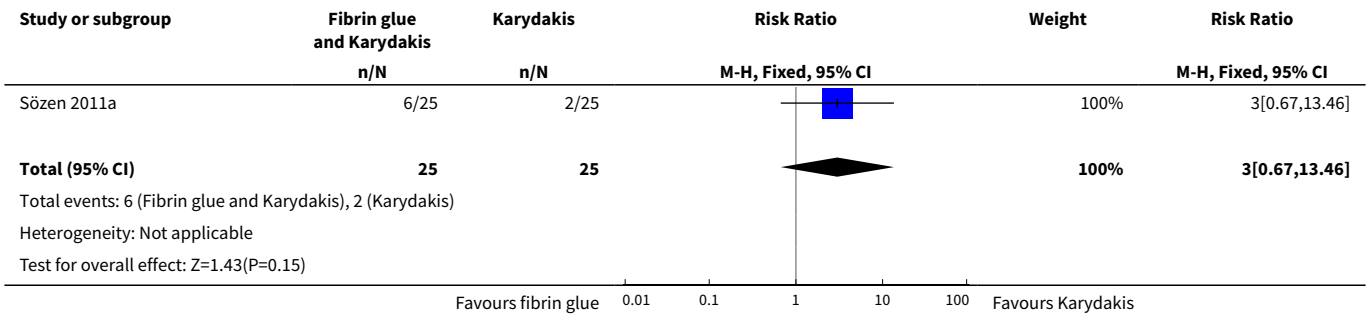
Study or subgroup	Fibrin glue and Limberg N	Mean(SD)	Limberg N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Altinli 2007	16	2 (0)	16	3.9 (0.6)		46.38%	-1.9[-2.19,-1.61]
Sözen 2011b	66	2 (0.6)	66	3.5 (0.6)		53.62%	-1.5[-1.7,-1.3]
Total ***	**82**		**82**			**100%**	**-1.69[-2.08,-1.29]**
Heterogeneity: Tau^2=0.06; Chi^2=4.79, df=1(P=0.03); I^2=79.12%							
Test for overall effect: Z=8.45(P<0.0001)							



Comparison 3. Fibrin glue and Karydakis flap versus Karydakis flap

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse event (seroma)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.67, 13.46]

Analysis 3.1. Comparison 3 Fibrin glue and Karydakis flap versus Karydakis flap, Outcome 1 Adverse event (seroma).



APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Pilonidal Sinus] explode all trees
#2 pilonidal:ti,ab
#3 #1 or #2
#4 MeSH descriptor: [Fibrin Tissue Adhesive] explode all trees
#5 (fibrin or fibrinogen or tissucol or tisseel or tissel or beriplast or crosseal or transglutine or fibrinogen):ti,ab
#6 #4 or #5
#7 #3 and #6 in Trials

Ovid MEDLINE

1 Pilonidal Sinus/
2 pilonidal.ti,ab.
3 1 or 2
4 Fibrin Tissue Adhesive/
5 (fibrin or fibrinogen or tissucol or tisseel or tissel or beriplast or crosseal or transglutine or fibrinogen).ti,ab,rn.
6 4 or 5
7 3 and 6

Ovid Embase

1 Pilonidal Sinus/
2 pilonidal.ti,ab.
3 1 or 2
4 Fibrin Tissue Adhesive/
5 (fibrin or fibrinogen or tissucol or tisseel or tissel or beriplast or crosseal or transglutine or fibrinogen).ti,ab,rn.
6 4 or 5
7 3 and 6

EBSCO CINAHL Plus

S7 S3 AND S6
S6 S4 OR S5
S5 TX (fibrin or fibrinogen or tissucol or tisseel or tissel or beriplast or crosseal or transglutine or fibrinogen)
S4 (MH "Fibrin Tissue Adhesive")
S3 S1 OR S2
S2 TX pilonidal
S1 (MH "Pilonidal Cyst")

Clinical trials databases and OpenSIGLE (keywords to maximise sensitivity)

fibrin OR pilonidal

Appendix 2. 'Risk of bias' tool

Random sequence generation

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.

Criteria for a judgement of low risk of bias.

The investigators describe a random component in the sequence generation process such as:

- referring to a random number table;
- using a computer random number generator;
- coin tossing;
- shuffling cards or envelopes;
- throwing dice;
- drawing of lots;
- minimisation*.

*Minimisation may be implemented without a random element and this is considered to be equivalent to being random.

Criteria for the judgement of high risk of bias.

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:

- sequence generated by odd or even date of birth;
- sequence generated by some rule based on date (or day) of admission;
- sequence generated by some rule based on hospital or clinic record number.

Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, for example:

- allocation by clinician's judgement;
- allocation by participant's preference;
- allocation based on the results of a laboratory test or a series of tests;
- allocation by availability of the intervention.

Criteria for the judgement of unclear risk of bias.

- Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'.

Allocation concealment

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Criteria for a judgement of low risk of bias.

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

- central allocation (including telephone, web-based and pharmacy-controlled randomisation);
- sequentially numbered drug containers of identical appearance;
- sequentially numbered, opaque, sealed envelopes.

Criteria for the judgement of high risk of bias.

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

- use of an open random allocation schedule (e.g. a list of random numbers);
- assignment envelopes used without appropriate safeguards (e.g. envelopes were unsealed, nonopaque or not sequentially numbered);

- alternation or rotation;
- date of birth;
- case record number;
- any other explicitly unconcealed procedure.

Criteria for the judgement of unclear risk of bias.

Insufficient information to permit judgement of 'low risk' or 'high risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

Criteria for a judgement of low risk of bias.

Either of the following:

- no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;
- blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

Criteria for the judgement of high risk of bias.

Either of the following:

- no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;
- blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Criteria for the judgement of unclear risk of bias. Any one of the following:

- insufficient information to permit judgement of 'low risk' or 'high risk';
- the study did not address this outcome.

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Criteria for a judgement of low risk of bias.

Either of the following:

- no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;
- blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Criteria for the judgement of high risk of bias.

Either of the following:

- no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;
- blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for the judgement of unclear risk of bias. Either of the following:

- insufficient information to permit judgement of 'low risk' or 'high risk';
- the study did not address this outcome.

Incomplete outcome data

Attrition bias due to the amount, nature or handling of incomplete outcome data.

Criteria for a judgement of low risk of bias.

Any one of the following:

- no missing outcome data;
- reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
- missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- missing data have been imputed using appropriate methods.

Criteria for the judgement of high risk of bias.

Any one of the following:

- reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;
- potentially inappropriate application of simple imputation.

Criteria for the judgement of unclear risk of bias. Either of the following:

- insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided);
- the study did not address this outcome.

Selective reporting

Reporting bias due to selective outcome reporting.

Criteria for a judgement of low risk of bias.

Either of the following:

- the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for the judgement of high risk of bias.

Any one of the following:

- not all of the study's pre-specified primary outcomes have been reported;
- one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for the judgement of unclear risk of bias.

- Insufficient information to permit judgement of 'low risk' or 'high risk'. It is likely that the majority of studies will fall into this category.

Other bias

Bias due to problems not mentioned above.

Criteria for a judgement of low risk of bias.

- The study appears to be free of other sources of bias.

Criteria for the judgement of high risk of bias.

There is at least one important risk of bias. For example, the study:

- had extreme baseline imbalance; or
- had a potential source of bias related to the specific study design used; or
- had an inappropriate influence of funders due to industry-initiated protocols;
- has been claimed to have been fraudulent; or
- had some other problem.

Or in cluster-randomised trials there is:

- recruitment bias (differential participant recruitment in clusters for different interventions);
- baseline imbalance;
- loss of clusters;
- incorrect analysis;
- comparability with individually randomised trials

Criteria for the judgement of unclear risk of bias.

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

Jon Lund: conceived the review question; developed and co-ordinated the protocol and review; wrote and edited the protocol and review; advised on the protocol and review; approved the final version of the protocol and review prior to submission; and is the guarantor of the protocol and review.

Samson Tou: developed the protocol and review; edited and performed part of the writing of the protocol and review; advised on the protocol and review; and approved the final version of the protocol and review prior to submission.

Brett Doleman: developed and co-ordinated the protocol and review; wrote and edited the protocol and review; advised on the protocol and review; and approved the final version of the protocol and review prior to submission.

John Williams: developed the protocol and review; edited and performed part of the writing of the protocol and review; advised on the protocol and review; and approved the final version of the protocol and review prior to submission.

Contributions of the editorial base

Joan Webster (Editor): edited the protocol; advised on methodology, interpretation and protocol content and approved the final protocol prior to submission.

Nicky Cullum: (Co-ordinating Editor): edited the review; advised on methodology, interpretation and review content and approved the final review prior to submission.

Gill Rizzello/Sally Bell-Syer (Managing Editors): co-ordinated the editorial process. Advised on interpretation and content, and edited the protocol and the review.

Reetu Child and Jo Elliott (Information Specialists): designed the search strategy, edited the search methods section and ran the searches.

Ursula Gonthier (Editorial Assistant): edited the plain language summary and the references.

DECLARATIONS OF INTEREST

Jon Lund has previously undertaken a randomised controlled trial on fibrin glue. He has applied for funding from HTA for a cohort study to evaluate the role of fibrin glue in pilonidal sinus disease

Samson Tou has no declarations of interest.

Brett Doleman received grants from the National Institute of Academic Anaesthesia for studies not related to this Cochrane Review. He previously won the Drager oral presentation prize which included payment from the AAGBI in a presentation competition.

John Williams has no declarations of interest.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol was not specific with regard to time of measurement of postoperative pain, therefore we presented the first measurement taken post procedure as is standard in trials of postoperative analgesics. In addition, we widened the inclusion criteria to include the use of fibrin glue as an adjunct to surgery since this is a related indication and the inclusion of these studies will not introduce bias. We also changed the title of the review for simplicity.

NOTES

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Combined Modality Therapy [methods]; Fibrin Tissue Adhesive [adverse effects] [*therapeutic use]; Pilonidal Sinus [etiology] [surgery] [*therapy]; Randomized Controlled Trials as Topic; Surgical Flaps; Surgical Procedures, Operative [adverse effects] [methods]; Time Factors; Tissue Adhesives [adverse effects] [*therapeutic use]; Wound Healing

MeSH check words

Humans; Young Adult